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The state versus amyloid-β: the trial of the most wanted criminal in Alzheimer disease

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Abstract

Investigators studying the primary culprit responsible for Alzheimer disease have, for the past two decades, primarily focused on amyloid-β (Aβ). Here, we put Aβ on trial and review evidence amassed by the prosecution that implicate Aβ and also consider arguments and evidence gathered by the defense team who are convinced of the innocence of their client. As in all trials, the arguments provided by the prosecution and defense revolve around the same evidence, with opposing interpretations. Below, we present a brief synopsis of the trial for you, the jury, to decide the verdict. **Amyloid-β: guilty or not-guilty**?

Keywords: Alzheimer disease; Cell death; Neurodegeneration; Neurotoxicity; Oxidative stress; Phosphorylated tau

The execution date for amyloid-β (Aβ) is now imminent. Vaccination of Aβ to Alzheimer disease (AD) patients, via an intranasal or intravenous route, is, in many people's opinion, going to improve the disease course by removing (killing) intracerebral Aβ senile plaques [112]. However, many others argue that a gross miscarriage of justice is about to occur and that executing Aβ still leaves the killer loose in the brain. The aim of this review is to, in effect, put Aβ on trial in front of a jury of readers by presenting evidence used by the prosecutors and defenders of Aβ. The prosecution, backed by public opinion eager to pin the blame on something, argues for guilt based on the fact that amyloid burden in the brain is correlated with dementia, that Aβ deposits are found in regions of the brain susceptible to neurodegenerative processes and that Aβ production is increased in all inherited forms of the disease [114]. Additionally, Aβ is a known killer of neurons in vitro [95,145] and surely must wreak the same carnage in the human brain. On the other hand, the defense, in the face of an overwhelming number of publications implicating Aβ as the major culprit in AD pathophysiology, argue for the innocence of Aβ as either an innocent bystander or a maligned protector of the brain [125]. The following represents a brief synopsis of the trial and, while the scientific debates continue to encircle this issue, it is our hope that this trial will define the questions that remain to be answered by both sides.

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1. The Prosecution

When investigating the crime scene of AD, namely the brain tissue of patients, it is quite obvious why Aβ is the primary suspect in disease pathogenesis. In fact, some of the earliest detectives studying the biochemistry of the AD brain determined that the Aβ peptide is the major constituent in two of the most distinctive pathologies, namely senile plaques and cerebral amyloid angiopathy [39,40,75]. Aβ is derived by proteolytic cleavage of Aβ precursor protein (AβPP), a protein of unestablished cellular function that has the general motif of a surface receptor [61,87]. Regardless of the fact that AβPP is a transmembrane protein in the neuronal plasma membrane, a secretory pathway in the Golgi apparatus processes the large majority of the protein before it ever reaches the cell surface [19,24,67]. While it was originally thought that Aβ represents an abnormal cleavage product, Aβ has been since been established as a normal product of neuronal AβPP metabolism, found in the cerebral spinal fluid (CSF) and serum of healthy individuals [45,118]. Differential activity between three different

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secretases, α, β and γ, at their specific cleavage sites yields a number of different products, including $A\beta_{1-40}$ and $A\beta_{1-42}$ [120]. While $A\beta_{1-40}$ is the predominant product of this proteolytic pathway, $A\beta_{1-42}$ is far more fibrillogenic in vitro and is the major Aβ species present in the core of senile plaques (both AD and non-AD related) [13,56]. The deposition of $A\beta_{1-40}$ and $A\beta_{1-42}$ into senile plaques likely begins with the nucleation of soluble $A\beta_{1-42}$ into fibrils followed by accumulation of normally soluble $A\beta_{1-40}$ [56]. Micro-environmental changes in the brain, such as pH, metal ion availability and oxidants, likely impact upon Aβ structural conformation and its deposition in amyloid plaques [6,123]. As of late a great deal of attention has also been focused on the fact that soluble forms of amyloid that are pre-fibrillar may also be involved in AD pathogenesis [69]. However, soluble forms of Aβ, including oligomers, correlate quantitatively with the number of senile plaques [130] and, therefore, all of the prosecution's (and defense's) arguments apply equally to all forms of Aβ.

The destructive nature of Aβ is evident from a close examination of histological preparations in the immediate vicinity of senile plaques revealing degenerative dendritic processes surrounding and infiltrating the plaques [36]. Additionally, regions severely affected by disease, including the hippocampus and frontotemporal cortices, show colocalization between Aβ plaques and neuronal cell death [107]. This led investigators to explore whether Aβ is toxic to neurons in both in vitro culture assays and in the intact brain of animals. The results of these experiments at first seemed extremely contradictory, stemming from lot-to-lot variability in the peptide and the lack of proper control over whether Aβ was aggregated into fibrils of β-sheet conformation [28]. Nonetheless, it is now established that fibrillation of Aβ is required to obtain neurotoxic effects [71,97,146] and that it is inherently toxic to neurons and clonal cell lines in culture [95,145]. Toxicity of the peptide has been shown to reside in between amino acids 25 and 35 [98]. The neurotoxicity of the peptide in vivo was likewise assessed by infusion of the peptide in a variety of animal models. Notably, intracortical injection of $A\beta_{1-42}$ or $A\beta_{25-35}$ fragments into aged rats or primates produced lesions reminiscent to those seen in AD patients [66]. In vivo injection of Aβ into the brain also led to neurodegeneration and dystrophic neurites in hippocampal neurons [95,96].

The source of Aβ toxicity has yet to be established, however, a number of theories have been advanced. The possibility that Aβ may act through a cell surface receptor and thereby trigger an intracellular signaling cascade, while not being eliminated as a possibility, is supported by little experimental evidence. Numerous studies have since supported the idea that an oxidative event is critical for Aβ toxicity (reviewed in [76]). It is thought that the peptide is capable of generating reactive oxygen species (ROS), which is supported by the fact that Aβ peptides can induce the generation of H_2O_2 [48,54,55], can stimulate inflammatory cells to produce ROS [1,15,81,135] and that neurotoxicity can be attenuated by administration of anti-oxidants and free radical scavengers, such as Vitamin E [9]. The prooxidant potential of Aβ also is supported by in vivo evidence where deposits are associated with oxidative damage [7,122,124] and such damage is, like Aβ deposition [113], viewed as an extremely proximal event in disease pathogenesis [89,90]. However, while it is clear that Aβ, either directly or indirectly, promotes oxidative stress and that toxicity can be attenuated by anti-oxidants, the precise mechanism by which amyloid deposition leads to increased oxidative stress remains elusive. Indeed, while studies have suggested that the neurotoxicity of aggregated Aβ is mediated by its ability to induce oxidative stress via the spontaneous generation of free radicals and ROS [48], this proposition has been questioned on theoretical and methodological grounds [31,110,133]. Instead, it now appears that the oxidant effects of Aβ are mediated by its interaction with redox-active metals such as iron and copper since chelation treatment of Aβ significantly attenuates toxicity [109]. Significantly, Aβ has an unusually high affinity for both iron and copper [6,29,53] and is capable of reducing these metals with subsequent production of hydrogen peroxide and oxidized amyloid [54,55]. The relevance of this mechanism to disease pathogenesis is highlighted by the association of redox active metals with senile plaques in AD [111,123]. In addition, the deposition of this normally soluble cellular protein promotes a chronic inflammatory response of the AD brain, whereby activated microglia release ROS as part of the respiratory burst (reviewed in [8]). Therefore, Aβ likely has much to answer for with regards to the oxidative damage observed in the AD brain.

Perhaps the strongest evidence for the crucial role played by Aβ in AD pathogenesis has been the characterization of the mutations that underlie familial early onset cases of the disease. All of these inherited mutations directly or indirectly affect the processing and accumulation of Aβ. The most straightforward form of familial Alzheimer disease (FAD) is caused by point mutations in AβPP in regions that are involved in the proteolytic processing of the peptide [41,70]. It is thought that these mutations accelerate the onset of AD into the fourth decade by increasing the ratio of $A\beta_{1-42}/A\beta_{1-40}$, thereby increasing the relative amount of the more fibrillogenic form [128]. A double mutation at positions 670/671 (Swedish mutation) increases the production of total Aβ and thereby increases the load of $A\beta_{1-42}$ without changing the relative ratio [18,23]. The fact that an increase in total Aβ load can accelerate the deposition of Aβ is supported by the neuropathology demonstrated in patients with Down syndrome, a disorder caused by trisomy of chromosome 21, where the AβPP gene is localized. It is thought that the overexpression of AβPP in these individuals [44] causes the formation of Aβ plaques very similar to those seen in the AD brain. The most common form of FAD is caused by mutations in one of the two presenilin genes (PS1 on chromosome 14 or PS2 on chromosome 1) (reviewed in [43]). While the function of the presenilin genes are not completely elucidated, it is known that the presenilin proteins localize to the endoplasmic reticulum and Golgi apparatus [65] and form stable complexes with AβPP [142]. Most importantly however, missense mutations in the presenilin genes likewise increase the ratio of $A\beta_{1-42}/A\beta_{1-40}$ [25,131]. Finally, it has been demonstrated that one allele of the apolipoprotein E gene, namely ApoE4 predisposes individuals to the development of late-onset AD [26]. Of the three alleles (also including ApoE2 and ApoE3), ApoE4 has the greatest affinity for Aβ, is found associated with senile plaques and is thought to accelerate fibrillogenesis [141]. Interestingly, ApoE2 is capable of inhibiting the formation of fibrils and is protective against the development of AD [27].

This strong evidence implicating Aβ in AD pathogenesis led to the supposition that generation of transgenic animals either over expressing AβPP or containing a mutation in AβPP that affects processing of the full length protein thereby leading to an increase in the $A\beta_{1-42}/A\beta_{1-40}$ ratio, may mimic the symptomatology of AD. Taken as a group, the various transgenic mice strains that have been produced have demonstrated that overexpression of AβPP or overproduction of the $A\beta_{1-42}$ peptide fragment is sufficient to cause deposition of the peptide into senile plaque-like structures and may in fact be responsible for at least some of the neurodegeneration in AD (reviewed in [50]). Indeed, despite the fact that each of the different constructs introduced yielded somewhat different phenotypes, some aspect of AD pathophysiology are apparent in each. For example, Games et al. created a transgenic mouse expressing human AβPP with the Val717Phe mutation at 10 times the endogenous level and these animals developed amyloid plaques in the hippocampus, cerebral cortex and corpus collosum by 6–9 months of age and also show synaptic loss and astrocytosis, although they show no behavioral abnormalities [35]. Among the first models to demonstrate behavioral changes reminiscent of those seen in AD, overexpressed AβPP containing the Swedish double mutation (Lys670Asn/Met671Leu). In addition to a marked increase in levels of Aβ in the CSF and deposition of amyloid plaques, these mice demonstrated marked deficits in spatial learning, as demonstrated by Morris water maze, by the age of 9 months [52]. Although no neurotoxicity was observed in these mice, it is thought that their impaired spatial learning, which is correlated with long-term potentiation (a model for memory), is related to synaptic loss. Interestingly, these mice also displayed oxidative stress in association with the plaques, much like that seen in AD [124]. Neurotoxicity has also been seen accompanied by an increased mortality rate, with 50% of mice dying by 12 months of age compared to an average of 24 months in controls, in mice overexpressing AβPP [68]. Although there are differences in the details of these studies, it is clear that Aβ can independently cause AD-related pathology and some behavioral defects.

Taken together, the aforementioned evidence clearly points the suspicion of doubt at Aβ as being an instrumental, if not the sole, culprit for causing disease.

2. The Defense

It is obvious that proponents of the causative role of Aβ in AD have a great deal of evidence in their arsenal and the preceding discussion would be sufficient to convince most juries of its guilt. Unfortunately, however, much of this evidence is circumstantial and in many cases the prosecution failed to discuss the caveats that create uncertainties as to the role of Aβ in AD. While we by no means intend to suggest that Aβ plays a negligible role in disease pathogenesis, it is very unlikely that the peptide is the main mediator of neurodegeneration.

The first, and perhaps most poignant, argument is the fact that deposition of Aβ into senile plaques is by no means specific to AD patients and in fact seems to be characteristic of normal aging [30]. The incidence of amyloid plaques in control individuals increases with age, as does the incidence of AD, and the number of plaques in cognitively normal individuals can rival those seen in advanced disease [74]. Even within those patients with AD, there is only a weak correlation between the burden of Aβ and neuronal loss or cognitive impairment [30,86]. Additionally, increased amyloid production and deposition is observed in response to injury to the central nervous system, including ischemia and head trauma [37,38,106]. Also, despite marked amyloid deposition in the brains of Down syndrome patients by the fourth decade, there is little evidence of further cognitive decline. Therefore, it appears that Aβ deposition is insufficient to develop full fledged AD. Rather it seems that Aβ may be produced in the disease as a cellular protective factor to compensate for the primary insult that causes AD [58,59,125]. This is not to imply that, in attempting to respond to cellular stresses, Aβ does not produce some cellular destruction while maintaining the integrity of the whole. However, it does require an underlying pre-existing stress, i.e. the presumable causative insult of AD.

A review of the literature would indicate that the underlying stress is an energetic one, since a shortage of energy supply (and Ca(II) overload) induces an upregulation of AβPP expression. Ischemia, hypoglycemia and traumatic brain injury, a condition that has been shown to put neurons under metabolic stress [143], all upregulate AβPP and its mRNA in animal models and culture systems [46,57,83,115–117,147]. Not only does energy shortage and Ca(II) dysregulation promote AβPP expression, but they also route the metabolism of AβPP from the non-amyloidogenic to the amyloidogenic pathway. Inhibition of mitochondrial energy metabolism alters the processing of AβPP to generate amyloidogenic derivatives [34,77], while oxidative stress has been shown to increase the generation of Aβ [32,82,93]. Consistent with this response Aβ has been detected in the human brain several days after traumatic brain injury [38]. This fits well with the role of AβPP as an acute phase reactant upregulated in neurons, astrocytes and microglial cells in response to inflammation and a multitude of associated cellular stresses including axonal injury [11,38], loss of innervation [138], excitotoxic stress [92,132], heat shock [22], oxidative stress [32,144], aging [49,88,134] and inflammatory processes [12]. Other pro-inflammatory stimuli that mediate the synthesis and release of AβPP include IL-1β [16,42] and TNFα converting enzyme [17]. The increased expression of AβPP by these stress conditions is likely a result of decreased energy supply.

The increased generation of Aβ under conditions of energetic stress may therefore be a response to the oxidative challenge observed in the brain in AD and following injury. In this vein, Aβ may in fact play a protective role. In support of this claim, the Aβ amyloid burden of the AD-affected brain has been shown to be significantly negatively correlated with oxidative stress markers [29,89,90] and in situ, soluble Aβ levels are inversely correlated with synaptic loss [72]. This argues against the neurotoxic role of Aβ in vivo, as does the fact that cultured neurons can be cultured directly on top of isolated Aβ plaques with out any notable toxicity [20]. Some have suggested that the in vitro toxicity that has been sporadically shown in culture, and very unreliable in animal models, may in fact be an artifact of culture and not intrinsic to the peptide itself [109]. Notably, Aβ appears to blunt oxidative stress in vivo [90,91] likely acting as an anti-oxidant [14]. Moreover, nanomolar concentrations of Aβ can block neuronal apoptosis following trophic factor withdrawal [21]. These findings are consistent with the trophic and neuroprotective action of Aβ at physiological concentrations in deprived conditions and neonatal cells that have been reported during the last decade [9,60,64,73,100,119,127,129,139,140,145]. Aβ also has been shown to protect neurons from death following injection of saline or iron [10] and protect lipoproteins from oxidation in cerebrospinal fluid and plasma (the mechanism of which is thought to involve metal ion sequestration) [6,62,63]. Moreover, Andorn and Kalaria [2] recently showed that low concentrations of Aβ possess significant anti-oxidant activity in an ascorbate-stimulated-lipid-peroxidation assay of post-mortem human brain membrane preparations. Together, these data provide a plausible physiological explanation for the increased generation of Aβ in AD and following head trauma, one that is aimed at reducing oxidative damage thereby preventing ROS-mediated neuronal apoptosis [105] and promoting neurite outgrowth.

Neurons are particularly vulnerable to oxidative stress as a consequence of high oxygen utilization, the high unsaturated lipid content of neuronal membranes and the post-mitotic nature of primary neurons. As a result, the balance between the production of ROS and anti-oxidant defenses are essential for proper neuronal function. Normally, anti-oxidant defense systems prevent any damage potentially produced by oxygen radicals. However, in cases of age related neurodegeneration, there is considerable oxidative imbalance, as demonstrated by accumulation of reversible and permanent alteration of cellular proteins and nucleic acids (reviewed in [108]). Given the fact that Aβ has been associated with the production of free radicals, it is essential to consider the spatio-temporal relationship between oxidative stress phenomena and Aβ deposition. Notably, oxidative stress is found in normal appearing susceptible neurons in AD brain and seems to be inversely correlated with Aβ deposition [89,90]. It therefore seems unlikely that Aβ accumulation is sufficient to explain the oxidative imbalance. Vulnerable neurons also display cell cycle abnormalities that are uncharacteristic of terminally differentiated neuronal populations. Despite the fact that successful nuclear division has yet to be demonstrated, a large number cell cycle regulators, both drivers and inhibitors of the cell cycle checkpoints, have been found in association with AD lesions and normal-appearing susceptible neurons [3–5,47,78–80,84,85,101–104,121,136,137,148–151]. Although the precipitating factors for this type of regulation have yet to be elucidated, a number of other AD-related phenomena can be linked to cell cycle abnormalities, including tau hyperphosphorylation, increased production and processing of AβPP and oxidative stress (reviewed in [104,108]).

Perhaps the strongest evidence for the role of Aβ in AD is that each of the familial forms of the disease involve a mutation or polymorphism of genes that are directly involved in AβPP processing (see above). A tremendous amount of effort and resources have been dedicated in the past several decades to determining the mechanism of disease of these mutations. While this line of research has been fruitful in characterizing FAD, it has proven only marginally useful to our understanding of sporadic AD, which by far represents the majority of cases. For example, mutations in AβPP have been identified in only 20–30 families world wide and represent less than 0.1% of the 15 million known cases of AD. Mutations in both presenilin 1 and 2, which are the most common genetic determinant of AD, only contribute an additional 120–130 families. While it is clear that mutations in these proteins involved in AβPP processing are capable of inducing amyloid neuropathies and dementia, no aberrant neurologies are observed usually for many decades, and even then, this is likely a result of the advanced deposition of Aβ in these individuals (the joint result of increased Aβ concentration and microenvironmental conditions) leading to the chronic neuroinflammation associated with the disease.

The prosecution's claim that the positive correlation between ApoE4 genotype and incidence of AD supporting a causative role for Aβ is likewise flawed. While it is true that ApoE4 has the greatest affinity for Aβ, is found associated with senile plaques and is thought to accelerate fibrillogenesis [141], this is not the sole or even the major physiological role of ApoE proteins. In the periphery, it is known that ApoE helps to regulate the transport and metabolism of lipids. It is also well established that the level of ApoE is elevated in response to injury in the peripheral and central nervous system [51] and, like Aβ, ApoE may thereby serve a protective role after ischemia or traumatic brain injury by distributing phospholipids and cholesterol to injured neurons [99]. ApoE may also protect against oxidative injury and prevent the accumulation of lipid peroxidation end products, such as hydroxynonenal, which are prominent features in AD and acute brain injury. In this vein, several studies showed that patients with homozygous ApoE4 genotype have longer periods of unconsciousness and higher incidence of post-traumatic coma following severe traumatic brain injury [33,126]. In short, ApoE4 predisposes patients for any number of neurodegenerative processes and is another factor that is completely unspecific to AD. Therefore, much like in acute injury, ApoE4 may be associated with a higher incidence of AD because it is less efficient in protecting neurons from the causative insult and therefore may have very little to do with its affinity for Aβ.

In sum, the defense argues that Aβ simply represents an innocent bystander rather than the culprit of disease [94,125].

3. Note added in press

Since the article was originally written, the removal of Aβ from patients with AD has been attempted as a therapeutic strategy. The technique involved immunizing patients with Aβ, a strategy which showed promise in reducing plaque burden in transgenic mice [112]. However, the clinical trials were suspended in March of 2002 when many patients developed acute exacerbation of symptoms, including confusion and inability to perform tasks [153–155]. While Elan Pharmaceutical Corporation has yet to release the details of the trials [152], one wonders whether this is major victory for the defense who said all along that Aβ was a much maligned protector of the brain and that removal would only serve to increase injury [58,59,94]. However, unfortunately, there are no rules against double jeopardy in science and Aβ will surely be accused and brought to trial again.

4. Concluding remarks

AD is a devastating condition and patients, caregivers, clinicians and scientists are eager to find the culprit and cure the disease. Whether Aβ is the culprit, as argued by the prosecution, or a bystander, as argued by the defense, is clearly important to decipher. All investigations start with multiple suspects, even multiple prime suspects, and it is the hope of all involved that we have the answer soon and can put this killer to rest.

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